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FOR

# THERMAL REGULATION OF FLUIDIC SAMPLES WITHIN A DIAGNOSTIC CARTRIDGE

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# THERMAL REGULATION OF FLUIDIC SAMPLES WITHIN A DIAGNOSTIC CARTRIDGE

## DESCRIPTION OF THE INVENTION

### Field of the Invention

[001] The present invention is related to an apparatus and method for controlling temperature in a reaction vessel. More particularly, the invention relates Point-of-Care ('POC") analytical devices with thermal regulation of reactants in a cartridge for body fluid diagnostics. The invention uses a localized heat source capable of emitting electromagnetic radiation, such as light emitting diodes ("LED"s) and vertical cavity surface emitting lasers ("VCSEL"s), capable of generating internal heat, such as resistive, inductive and Peltier heaters, or capable of external heating.

### Background of the Invention

[002] Conducting chemical reactions on the microscopic scale in a miniature analytical device, while being able to precisely vary reaction parameters such as concentration and temperature have been made possible by trends in microfluidics and combinatorial chemistry. Such control requires thermal regulation using a localized heat source on the miniature analytical device.

[003] The term "miniature analytical device" refers to a device for conducting chemical and biological analytical tests ("assays") on a smaller scale as related to bench-top analytical equipment. Because such devices are small and light weight, they can be portable as well as modular with

disposable and reusable portions. The portability of such devices makes it possible to carry out such reactions near the patient, at the point of care, rather than in the laboratory.

[004] The term "localized heat source" refers to a source of heat which is proximate to the substance to be heated. Such a source can comprise of multiple point sources of heat. One particular area where being able to carry out chemical and biological reactions on a miniature device in the field has great importance is the area of medical diagnostics of bodily fluids such as blood.

[005] Medical diagnostics of bodily fluids can involve several assays using a variety of assay elements. The term "reactants" refers to chemicals involved in a synthetic reaction, or assay elements such as body fluid samples (such as blood), washes, and reagent chemicals. Sensing methods for blood metabolites such as $pO_2$, $pCO_2$, $Na^+$, $Ca^{++}$, $K^+$, glucose or clinical parameters such as blood pH, hematocrit, and coagulation and hemoglobin factors include electrochemical, chemiluminescence, optical, electrical, mechanical and other methods.

[006] The home-care or self-analysis by patients had been facilitated by miniature analytical devices, which can analyze body fluids. Many POC tests are performed using capillary whole blood. Typically, a drop of blood for analysis is obtained by making a small incision in the fingertip or forearm, creating a small wound, which generates a small blood droplet on the surface of the skin. Moving tests closer to the patient's side by using miniature analytical devices, improves both the testing process and the clinical data

information management, which in turn has a dramatic impact on both patient outcomes and costs to the health care system.

[007] Some of the desired biochemical tests require a specified and stabilized temperature for accurate and reportable measurements. Prior solutions to the problem of controlled temperature included large instruments with substantial temperature-controlled zones that required significant electrical power to provide heating.

[008] The term "heating" refers to adding heat to a substance to raise its temperature and removing heat from a substance to reduce its temperature. The term "thermal regulation" refers to modifying heating to increase, decrease, or maintain the temperature of a substance to a desired temperature.

[009] Thermal regulation of reactants or assay elements can be achieved through bulk heating of the cartridge using heaters such as electrical resistance heaters, Peltier heating and cooling cells, air heaters, or infrared heaters. These bulk-heating systems are usually large, and have generous energy supplies. POC devices require smaller volumes than bench-top systems. POC device volumes range between $1 \times 10^{-1}$ and $1 \times 10^{3}$ microliters. More specifically, a POC diagnostic devices can heat volumes of 1-5 micro liters of assay elements, such as a blood sample, and/or 100-500 micro liters of assay elements, such as reagents. Restricting the volume to be heated to the temperature-controlled zones reduces the amount of heat required and facilitates localized heating.

[010] For a POC device to be truly portable, power management is a critical issue. One method of limiting power usage is to localize heating to only those zones where heating is necessary. Localized heating provides lower power consumption and more rapid attainment of a specified reaction temperature. Such a localized approach to heating has the added benefit of minimizing the cost of manufacturing the disposable cartridge for diagnostic analysis. The localized heating elements needed for the rapid transmission of heat and the regulation of temperature can be localized on the POC device and the assay elements to be heated can be localized on the disposable cartridge. Such efficiencies in power usage can save battery life.



[011] There have been attempts at designing thermal regulation devices for miniaturized reaction chambers for synthetic and diagnostic applications such as PCR amplification, nucleic acid hybridization, chemical labeling, and nucleic acid fragmentation. These attempts have focused on bulk resistive heating. Bulk resistive heating requires direct contact between the POC device and the cartridge with the reactants. Bulk resistive heating is inefficient and slow compared to localized heating because it heats the surrounding environment as it heats the assay elements contained within the cartridge. Bulk resistive heating increases the time it takes to increase the temperature of the reactants because the cartridge must be heated to the desired temperature. Localized heating shortens the distance over which external heating occurs, bypasses the cartridge with radiation directed to the reactants, or heats from within the reactants.

[012] It is accordingly a primary object of the invention to localize heating to specific temperature-controlled zones in a cartridge using electromagnetic radiation, internal heat, or external heat. The advantages are that such localized heating does not require direct contact with the entire cartridge. The localized energy provided by these heat sources can be easily and accurately manipulated so that the amount of energy directed towards portions of the cartridge can be finely tuned and controlled so that the desired temperature is rapidly achieved and maintained. Heating by localized energy mainly affects the reactants themselves, rather than the entire cartridge and/or the environment.

## SUMMARY OF THE INVENTION

[013] In accordance with the invention, a miniature analytical device with thermal regulation comprises of a localized heat source to regulate the temperature in an array of temperature-controlled zones containing reactants such as assay elements for body fluid analysis. Thermal regulation through electromagnetic radiation can be achieved through the absorbance of irradiation by molecules of the reactants or assay elements, for example, the water molecules in the body fluid sample. Electromagnetic radiation can be emitted by LEDs, VCSELs, or microwave sources. Resistive, inductive and Peltier heaters positioned within or adjoining the reactants can generate internal heat. External heat can be generated by resistive heaters in contact with the cartridge which in turn heat the reactants.

[014] The electromagnetic radiation in the form of an infrared illumination emitter can be configured as an array of infrared light sources,

such as infrared lamps, infrared lasers, infrared laser diodes, LEDs or VCSELs positioned such that they correspond to the array of temperature-controlled zones. These infrared light sources can generate infrared light at different wavelengths ranging between 0.775 and 7000 micrometers. A power supply can be coupled to the infrared light sources to provide a sufficient drive current to regulate the temperature-controlled zones and to modulate using a controller so that the miniature analytical device can rapidly increase and maintain the temperature of the reactants in the temperature-controlled zones.

[015] A method for heating includes heating an array of temperature-controlled zones, measuring the temperature, modulating the localized heat source, and regulating the temperature. In another embodiment, the method can include a step of modifying at least one absorptive property of the reactants, including color, refractive index, or transmission path (by using shutters or an LED window).

[016] Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[017] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

## DESCRIPTION OF THE EMBODIMENTS

[018] Reference will now be made in detail to the present embodiments of the invention. Thermal regulation of the reactants can be accomplished through the use of electromagnetic radiation from an emitter. The term "emitter" refers to a non-contact electromagnetic radiation source including microwave, infrared, or ultra-violet light which manipulates intensity, direction, phase, color, and other properties of the light. In one embodiment, this electromagnetic radiation energy can be derived from an infrared light source, which emits light in the wavelengths known to heat water, which are typically in the wavelength range from about 0.775 to 7000 micrometers (775 to $7x10^6$ nanometers). For example, the infrared activity absorption bands of sea water are 1.6, 2.1, 3.0, 4.7 and 6.9 micrometers with an absolute maximum for the absorption coefficient for water at around 3 micrometers.

[019] The infrared wavelengths are directed to the temperature-controlled zones containing the reactants, and because the portion of the cartridge around the temperature-controlled zones can be made of a clear or translucent material, the infrared waves can act directly upon the reactants to increase or maintain the temperature in the temperature-controlled zone. The term "temperature-controlled zone" refers to the area of space in which the assay elements or reactants are contained for thermal regulation such that an increase in the temperature of such zone corresponds to an increase in the temperature of the assay elements or reactants. Although infrared heating of the assay elements can be the result of the cartridge itself absorbing the irradiation of the infrared light, infrared heating of the reactants is primarily

caused by the direct action of the infrared wavelengths on the reactants themselves.

[020] The portion of the cartridge containing the temperature-controlled zones can be made of a material that allows the penetration of infrared light wavelengths, such as quartz glass, glass, silicon, transparent plastics, and the like. In one embodiment, a lightweight inexpensive material that allows infrared light to pass through with little interference is desired for the disposable diagnostic cartridge.

[021] Alternatively, the infrared energy can be focused on the temperature-controlled zones by means of infrared transmissible lenses so that the sample is homogeneously irradiated. This technique avoids "hotspots" that could otherwise result in the creation of undesirable temperature differences and/or gradients, or the partial boiling of the assay elements. The homogeneous treatment of the temperature-controlled zones with infrared energy therefore contributes to a sharper and more uniform temperature profile for thermal regulation of the assay elements. Moreover, rapid increase in temperature can be facilitated if the miniature analytical device has a flat temperature-controlled zone exposing a majority of the assay element to the infrared light so that there exists a high ratio of surface area in contact with infrared light to volume of temperature controlled zone.

[022] Infrared heating can be effected in either one step, or numerous steps, depending on the desired application. For example, a particular methodology may require that the reactants be heated to a first temperature, maintained at that temperature for a given dwell time, then

heated to a higher temperature, and so on. As many heating steps as necessary can be included. The method can include measuring the temperature, measuring the concentration, modulating the localized heat source, and regulating the temperature. Alternatively, the method can include steps for modifying the optical absorptive properties of the reactants, including modifying their color. Alternatively, the method can include varying the wavelength of light whether within the infrared spectrum or in the microwave or ultraviolet spectrum.

[023] Similarly, each reactant can require a specified thermal regulation depending on the particular assay. The electromagnetic radiation emitter can be configured into an array of point sources of electromagnetic radiation. The miniature analytical device and the array of point sources of electromagnetic radiation allows many assays to be run simultaneously on one cartridge using a variety reactants. In one embodiment, a variety of assays can be run using pre-packaged assay elements, such as reagents, and one recently obtained assay element, such as blood.

[024] In one embodiment, an infrared emitter can be a single source with lenses and reflectors directing the light to the temperature-controlled zones. Alternatively, an array of infrared light emitters can be positioned so as to correspond to an array of temperature-controlled zones containing reactants to directly provide localized heating for each temperature-controlled zone with a corresponding infrared light source. The infrared light source may be any means known in the art for generating the desired range of wavelengths in the infrared spectrum. Typically, the heating means will be an

infrared source, such as an infrared lamp, an infrared diode laser, an infrared laser, an LED or a VCSEL. In one embodiment, LEDs or VCSELs can be used for their easy arrangement in arrays and low power consumption. The term "array" refers to any configuration on the miniature analytical device corresponding to the configuration of temperature-controlled zones on the cartridge to conduct thermal regulation for all synthetic and/or diagnostic reactions carried out on the cartridge. The infrared light source can be supplied drive current by a power supply and modulated by a controller such that the current from the power supply achieves the desired thermal regulation in the temperature-controlled zones.

[025] VCSELs can be formed by using for example a GaInAs, GaAlInP, Fabry-Perot, or ZnSe material system to generate infrared light at wavelengths of, for example, 980 nanometers and a beam diameter of 8-10 micrometers. The VCSELs are constructed on chips with for example grown diamond, AlN or plain copper substrates to control the incidental heat flux created on the miniature analytical device by generating the infrared light. VCSELs have 15-50% conversion efficiency between the power it takes to run the VCSEL to the infrared power generated. Moreover, VCSELs allow for measurement of the concentration of compounds by optical tests known in the art. The cartridge can be configured such that a transparent material bounds both sides of the temperature-controlled zone. On one side, the VCSEL emits infrared light to thermally regulate the reactants or assay elements. On the other side, the infrared light transmitted through the reactants or assay elements can be measured to determine the concentration of a material within

the reactants. The term “material” refers to the product-of-interest of the reaction whose concentration is to be measured or the analyte within the assay elements for which the assay is testing concentration.

[026] In one embodiment, concentration of a material in the reactants can be measured by measuring the electromagnetic absorption of the reactants as is well known in the art of spectrophotometry. In another embodiment, the temperature of the reactants can be measured by measuring the electromagnetic emission of the reactants as is well know in the art of spectrophotometry.

[027] In bench-top thermal regulation, assay elements such as blood have been heated to either 25°C or 37°C using infrared light energy. An added benefit of using optical energy such as infrared light consists of using optical means for measuring the temperature. Such means are well known in the art, and retain the benefit of non-contact between the miniature analytical device and the disposable cartridge. In one embodiment, the miniature analytical device can be configured with an array of temperature monitors to correspond to the temperature-controlled zones. The term “temperature monitor” refers to a device for measuring the temperature of the reactants or assay elements in the temperature-controlled zone, or measuring the temperature of the portion of the cartridge surrounding the temperature-controlled zone or the environment. A feedback loop, comprising of providing the measured temperature to the controller, modulates the power supply to drive the infrared light source so that the desired temperature is achieved with a smooth control curve and/or is maintained at the desired temperature.

[028] In one embodiment, the localized heat source comprises of internal heat that can be generated by resistive, inductive and Peltier heaters positioned within or adjoining the reactants. In one embodiment, these heaters can be arranged to in an array to correspond to the array of temperature-controlled zones. Resistive heaters use the effect of heating electrically resistive elements, by passing current through the elements. Inductive heaters use the effect of heating electrically conductive materials, such as metals, by inducing high frequency currents within the material. Peltier heaters use Peltier effect to generate heat by passing electric current through a bimetallic junction. In one embodiment, an array of electrical leads can be positioned to correspond to the array of heaters, such that the array of electrical leads on the miniature analytical device correspond to the heaters on the cartridge. In one embodiment, the heaters can comprise of discrete elements such as microbeads or filings, or continuous elements such as meshes, pads, or nets. These elements can be manufactured into the cartridge during the fabrication process to best position the elements in the vicinity of the temperature-controlled zones.

[029] In another embodiment, external heat can be generated by resistive heaters in contact with the cartridge, which in turn heats the reactants. These heaters can be arranged in a sandwich structure surrounding the broad, flat surfaces of the cartridge comprising a temperature-controlled zone such that the heaters are in close proximity or in contact with the cartridge at the temperature-controlled zones. Such placement minimizes the thermal path length and resistance through which

heat travels. The heaters can be arranged in an array to correspond with the array of temperature-controlled zones.

[030] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.